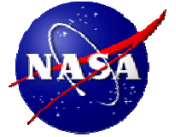


Overview of Space Radiation Health Risks with a Focus on Radiation-Induced Cardiovascular Diseases

Zarana S. Patel, Janice L. Huff, Lisa C. Simonsen



Future Manned Missions



International Space Station

- 2013-2020: 6-person crews, 180 days (nominal); 2-person crew 360 days in planning
- Approach limits for acceptable radiation risks after 1 to 3 missions

Lagrange Points

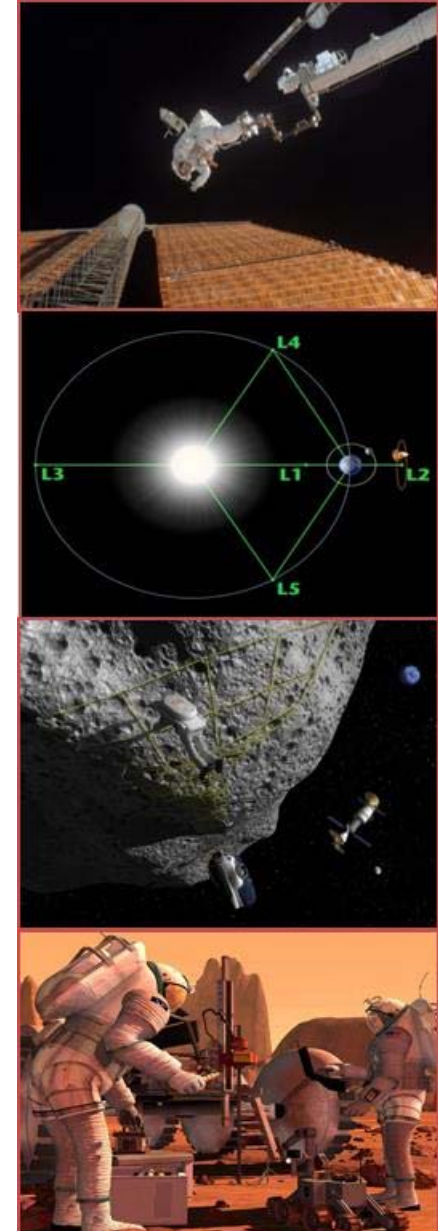
- Design Reference Mission currently being formulated
- Outside Earth's magnetosphere and radiation belts
- Galactic cosmic ray risks are major concern

Near Earth Objects

- Design Reference Mission currently being formulated
- Outside Earth's magnetosphere and radiation belts
- Galactic cosmic ray risks are major concern

Mars

- 2030 and beyond: 6-person crews, up to 1000 days
- Long deep space transit times
- Risks exceed NASA Permissible Exposure Limits (PELs) for cancer, and pose significant non-cancer risks



Integrated Radiation Protection Strategy Enables Human Mars Exploration

Long-Term Commitment across Research and Technology Required...

National Aeronautics and
Space Administration



Mission and Architecture Systems Analysis



Near Earth Asteroid Systems

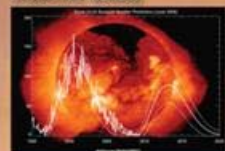
Mars NTV

In-situ Resource Utilization

Active Shielding Concepts

Environmental Modeling, Monitoring, and Prediction

Predictive Models



Precursor Data — MSL RAD



On-board Dosimetry— ISS TEPC

Crew Selection and Operations



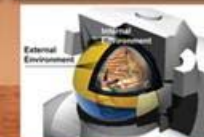
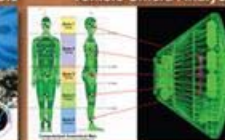
Human Digital Twin

Integrated Radiation Protection System Design and Analysis

Design and
Optimization Tools



Crew Exploration
Vehicle Shield Analysis



High Energy Nuclear
Physics and Transport

Radiobiology and Biological Countermeasures



NASA Space Radiation Lab at Brookhaven National Laboratory

X-ray vs. Heavy Ion
Track Damage to DNA

Leukemia induction
with GCR — Mouse Model

Innovative Multi-Purpose Shield Solutions



Heavy Ion Testing of
Inflatable Shield Prototype

Water Filled Composite
Shield Sections

Reconfigurable
Personal Shielding

Hydrogen
Storage BNNT

Advances benefit homeland security, cancer therapy, Earth observing and communication satellites, and commercial air safety

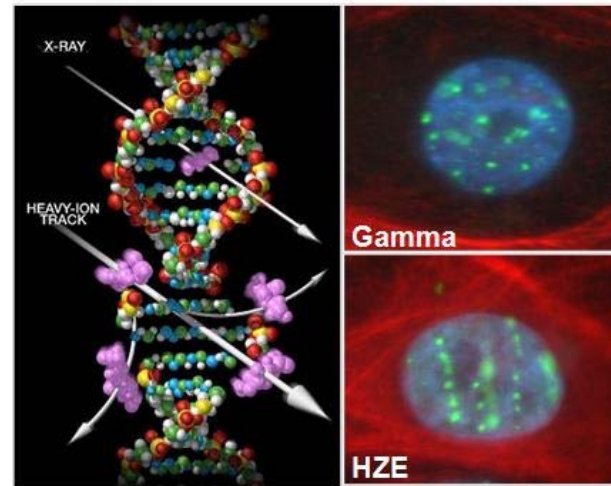
www.nasa.gov



The Space Radiation Problem

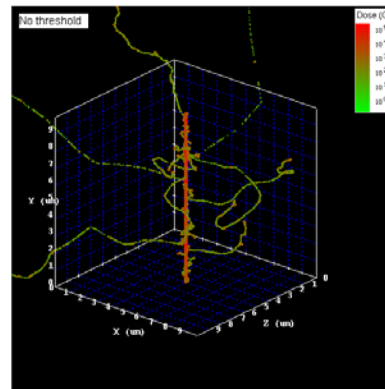
- Interplanetary crews will be exposed to a high LET radiation environment comprised of high-energy protons and heavy ions (HZE's) as well as secondary protons, neutrons, and fragments produced in shielding and tissue
- Heavy ions are qualitatively different from X-rays or Gamma-rays: High LET vs. low LET
 - Densely ionizing along particle track
 - Cause unique damage to biomolecules, cells, and tissues
 - Distinct patterns of DNA damage (mutation spectra, chromosome aberrations) and distinct profiles of oxidative damage
- No human data exist to estimate risk from heavy ions found in space
 - Animal and cellular models with simulated space radiation must be applied or developed
- Synergistic modifiers of risk from other spaceflight factors

DNA Damage



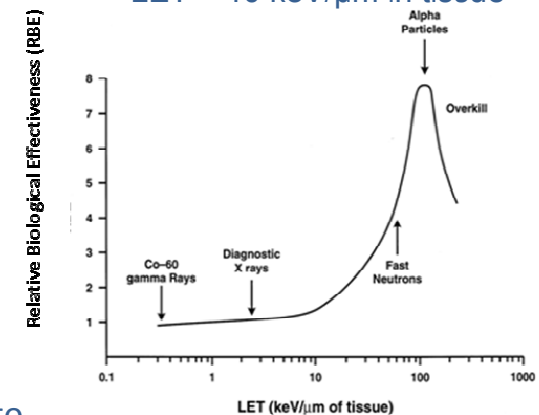
DNA Damage
 γ H2AX foci in EPC2-hTERT cells.
(Patel and Huff)

1 GeV/u ^{56}Fe nucleus
LET ~ 150 keV/ μm



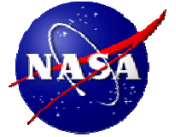
Qualitative differences due to track “core” and correlated tissue damage along a particle path.
(Plante, 2011)

High LET defined as
LET > 10 keV/ μm in tissue





Space Radiation Risks

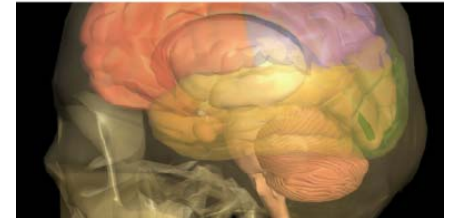
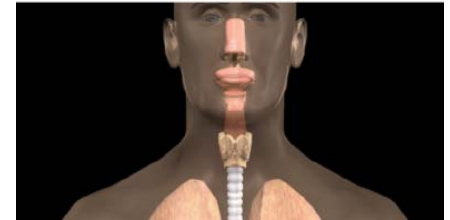


Risk of Radiation Carcinogenesis

- Morbidity and mortality risks; major driver for PELs

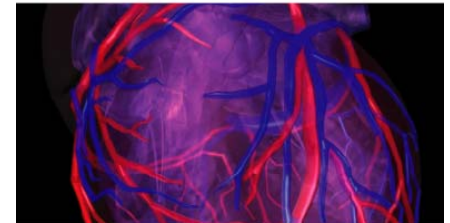
Risk of Acute (in flight) & Late Central Nervous System Effects

- Possible in-flight risks: altered cognitive function including short-term memory, reduced motor function, and behavioral changes which may affect performance and human health
- Possible late (post-mission) risks: neurological disorders such as Alzheimer's disease (AD), dementia, cerebrovascular disease or premature aging



Risk of Cardiovascular Disease and other Degenerative Tissue Effects

- Degenerative changes in the heart, vasculature, and lens
- Diseases related to aging, including digestive, respiratory disease, premature senescence, endocrine, and immune system dysfunction



Risk of Acute Radiation Syndromes due to Solar Particle Events

- Prodromal effects (nausea, vomiting, anorexia, and fatigue), skin injury, and depletion of the blood-forming organs



Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation

Risk of Degenerative Tissue Effects:

- Cardiovascular and circulatory changes
- Cataract formation

Other Health Effects:

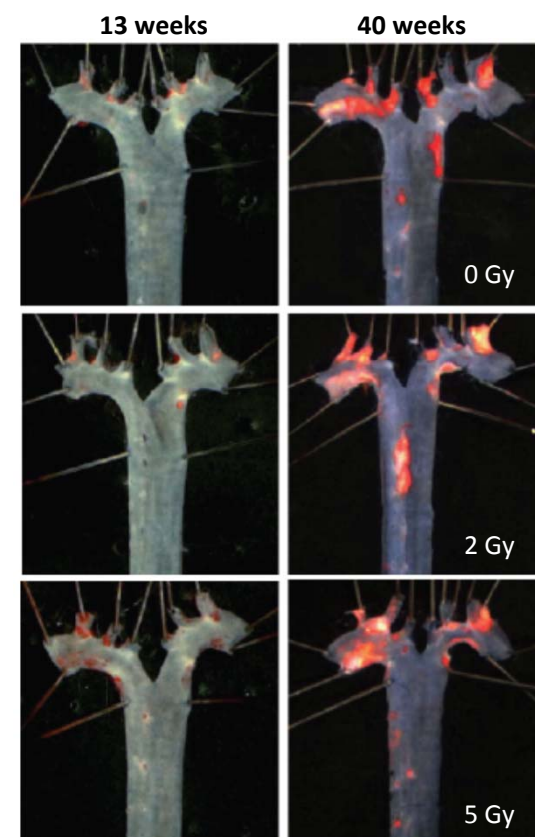
- Diseases related to aging, including digestive, respiratory disease, premature senescence, endocrine, and immune system dysfunction

Driving Evidence:

- Astronaut data (cataracts)
- Radiotherapy, environmental disasters, atomic bomb survivor data, radiation workers (CVD and others)
 - Data is confounded by life-style factors to larger extent than cancer, especially at low doses

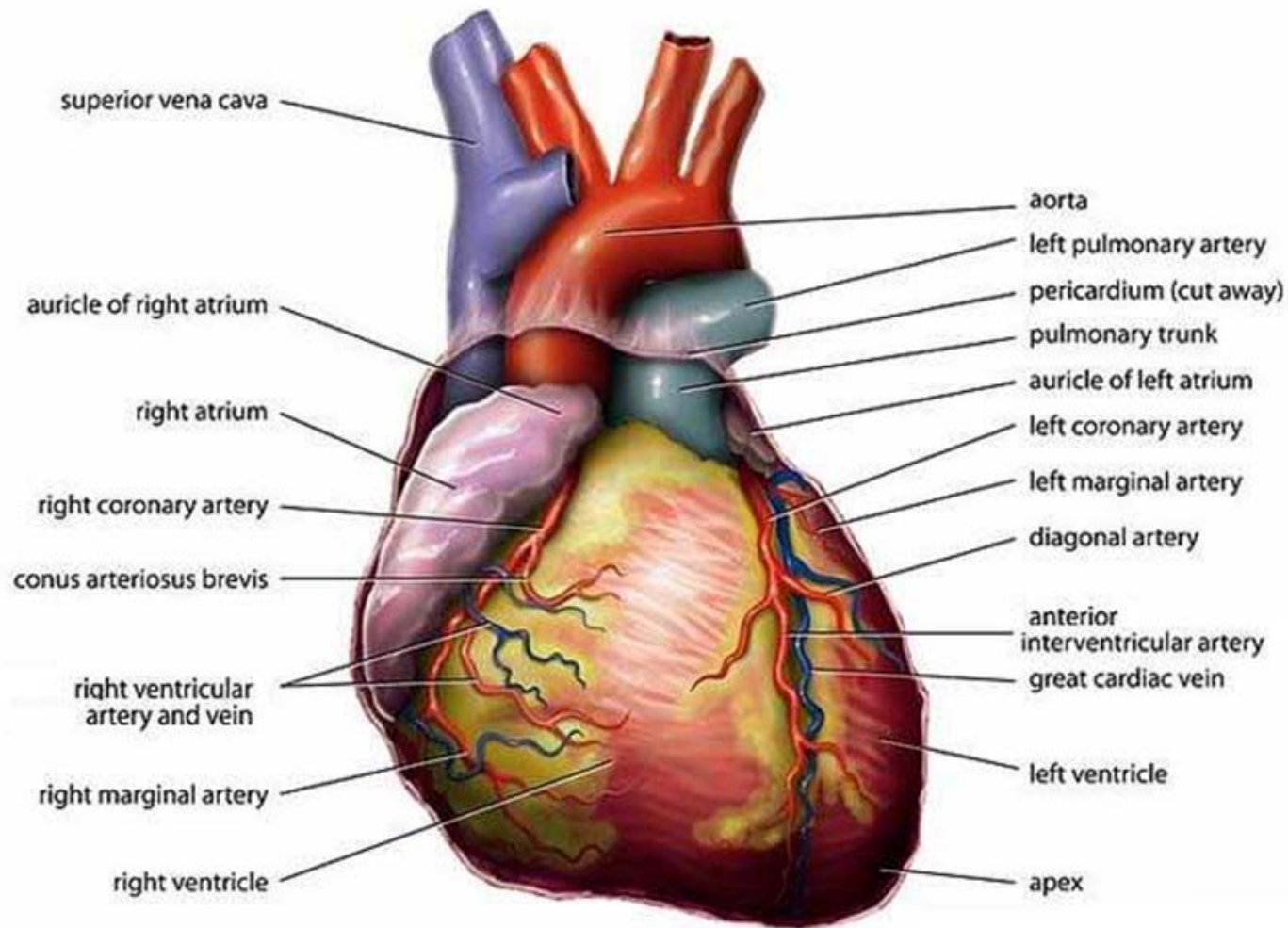
Risk Projections:

- Preliminary risk assessment models being formulated
- Recent studies suggest there may be low dose effects and distinct pathologies at low vs high dose suggesting mechanistic differences
- Impact of heavy ions largely unknown



Aortic lesions in apoE^{-/-} mice after ⁵⁶Fe irradiation (Kucik et al., Rad Res 2011)

Driving Evidence for Radiation-Induced CVD



Spectrum of Circulatory Diseases Related to Radiation Exposure

Main types of circulatory disease:

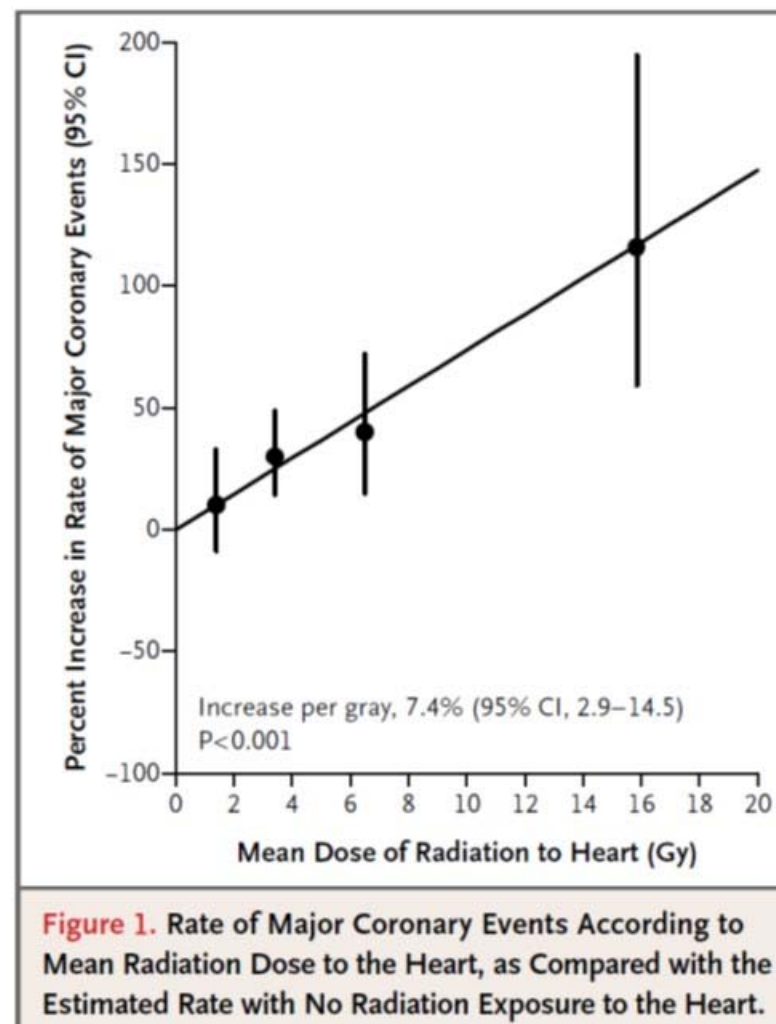
- Congenital heart disease. Includes a range of abnormalities in heart structure or function that are present at birth. Such conditions could potentially be caused by irradiation of the fetus but obstetric irradiation is carefully controlled
- Cardiac valve diseases. Include a variety of abnormalities to the heart valves including mitral stenosis and tricuspid regurgitation
- Hypertrophic cardiomyopathy. Increased muscle density in the heart leading to less effective pumping of the blood
- Cardiac Arrhythmias. Abnormally slow (bradycardia) or fast (tachycardia) beating of the heart often attributable to abnormalities in the electrical signaling that co-ordinates the beating of the four chambers of the heart
- **Pericarditis**. Inflammation of the pericardium, the membrane that surrounds the heart, most frequently attributable to infectious agents but also well established to be caused by high doses of radiation
- **Coronary heart disease/congestive heart disease**. Obstruction of the blood flow in the heart due to narrowing of cardiac vessels restricting blood and oxygen supply to the heart. In a mild form, this leads to **angina** where the reduced blood flow leads to discomfort. When blockage is severe, **myocardial infarction (heart attack)** occurs leading to acute heart failure
- **Stroke**. Interruption of the blood supply to the brain due to blockage or rupture of vessels. Loss of blood and oxygen to areas can lead to cell death and consequently permanent brain dysfunction. Two majors forms of stroke are recognized, ischemic stroke caused by blockage due to blood clots forming locally (**thrombotic stroke**) or fragments from distant clots lodging in the brain vasculature (**embolic stroke**)

→ The circulatory diseases subtypes that are considered to be affected by radiation exposure appear in bold text

Driving Evidence for High Doses > 5 Gy

Radiotherapy Data:

- High doses (>5 Gy exposures) associated with damage to the structures of the heart and to the coronary, carotid, and other large arteries including marked diffuse fibrotic damage, especially of the pericardium and myocardium, pericardial adhesions, microvascular damage and stenosis of the valves—damage observed in patients receiving RT as well as in experimental animals (Little 2013)
- Deterministic effect (tissue reaction)
- Mechanisms involve cell killing or inactivation of large # of cells – functional impairment



Driving Evidence for Moderate Doses 0.5 - 5 Gy

Life Span Study, Clinical, and Occupational Exposures :

- Moderate doses (0.5-- 5 Gy exposures) associated with atherosclerosis; micro and macrovascular damage
- Possibly a stochastic reaction
- Mechanisms may involve inflammation and oxidative stress, endothelial dysfunction/senescence

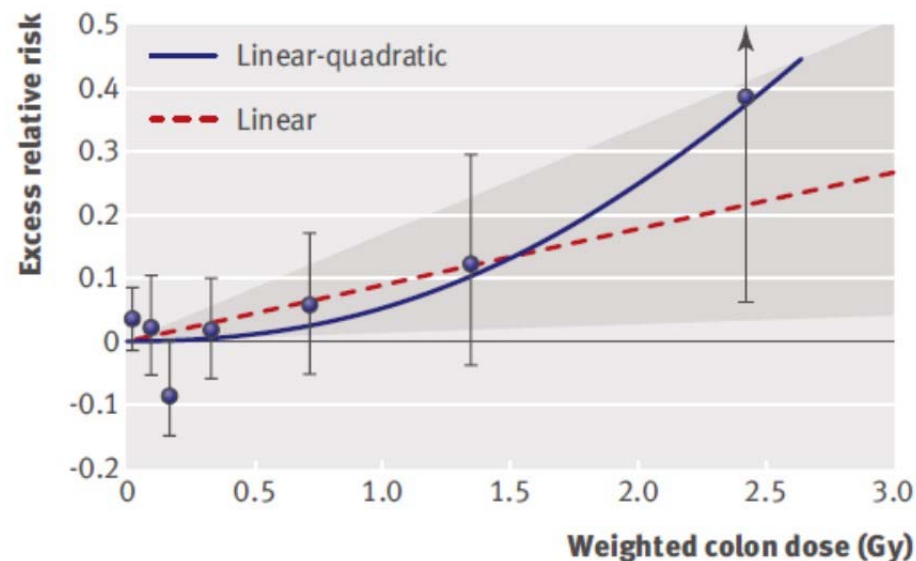


Fig 1 | Radiation dose-response relation (excess relative risk per Gy) for death from stroke, showing linear and linear-quadratic functions. Shaded area is 95% confidence region for fitted linear line. Vertical lines are 95% confidence intervals for specific dose category risks. Point estimates of risk for each dose category are indicated by circles

Driving Evidence for Moderate Doses 0.5 - 5 Gy

Table 1 Published epidemiological studies reporting on the association between mortality from heart disease and ionising radiation with doses in the range 0.5–5 Gy (or 0.5–5 Sv) and with good power to detect an association. Based on (5) and updated

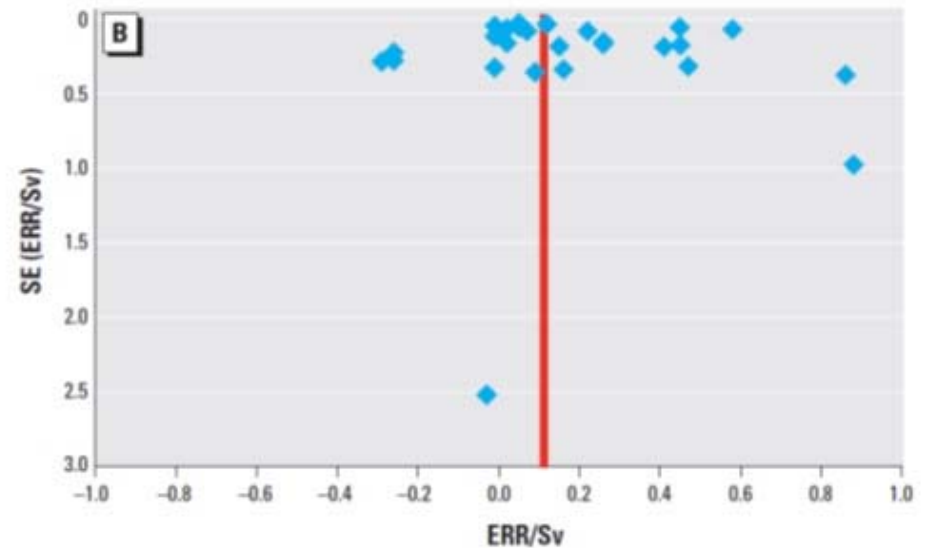
Population	Relation between mortality from heart disease and ionising radiation
Studies finding a significant positive association	
Life Span Study of survivors from atomic bombings of Hiroshima and Nagasaki, Japan ⁴	RR for heart disease increased by 17% (90% CI 8–26%; $P=0.001$) per Sv for deaths in period 1968–97, i.e. 23–52 years after exposure.
Radiologic technologists, USA ¹⁰	RR for heart disease, for deaths in period 1983–1997, 1.22, 1.00, 0.98, 1.00 for those starting work <1940, 1940–49, 1950–59, 1960+; P for trend 0.03. Cumulative doses probably up to 2 Gy for those starting before 1950.
Patients irradiated for peptic ulcer, USA ⁶	RR for heart disease 1.00, 1.00, 1.23, 1.54, 1.51 at 10+ years after exposure for those with average cardiac doses of 0, 1.6, 2.3, 2.8, 3.9 Gy; P for trend 0.01.
Chernobyl accident emergency workers, Russia ⁷	RR for heart disease increased by 41% (95% CI 5–78%; $P=0.02$) per Gy (no lag).
British Nuclear Fuels, UK ⁹	RR for heart disease increased by 70% (90% CI 33–111%; $P<0.001$) per Sv (with 15-year lag).
Studies not compatible with a positive association based on currently published data	
Radiologists, USA ¹¹	RR for heart disease compared with all male medical practitioners 1.20 and 1.18 for those registering during 1920–39 and 1940–69, respectively. RRs for cancer calculated on a similar basis were 1.54 and 1.22, respectively. Those registered in early period thought to have had lifetime doses of 2–20 Gy.
Patients with tuberculosis, USA ¹²	RR for all circulatory disease: 0.9 (95% CI 0.8–1.00; $P=0.05$) in exposed vs unexposed. Mean lung dose 0.84 Gy. Mean heart dose likely to be similar.
Radiologists, UK ¹³	RR compared with other doctors for all circulatory disease 0.79, 0.83, 0.98, 0.59 for those first registered <1920, 1921–35, 1936–54, 1955–79; P for trend >0.10. RRs for cancer calculated on a similar basis were 1.75, 1.24, 1.12, 0.71; P for trend <0.001. The trend for cancer has been interpreted as an effect of radiation. In the 1920s and 1930s doses may have been ~1 Gy per annum.
Uranium miners, Germany ⁸	RR for heart –35% (95% CI –70–0.9%; $P>0.10$) per Sv for deaths in period 1946–98 (with 5-year lag).
Other studies	
Patients with ankylosing spondylitis, UK ^{14,15}	RR for circulatory disease excl stroke: RR 0.97 (95% CI 0.70–1.33; $P>0.10$) in exposed vs unexposed. Mean lung dose 2.5 Gy. Mean heart dose likely to be similar.
Mayak, Russia ¹⁶	RR for all circulatory disease 1.01 (95% CI 0.90–1.15) in those with >1 Gy compared with <1 Gy (no lag).

^aRR: Death rate ratio.

Driving Evidence for Low Doses < 0.5 Gy

Meta-Analysis of Low Dose Studies:

- Low doses (< 0.5 Gy) associated with systemic effects, microvascular damage
- Possibly a stochastic reaction
- Mechanisms may involve non-targeted effects, kidney dysfunction, monocyte killing
- Confounding effects are large



Funnel plot of ERR/Sv versus SE of ERR for 4 main circulatory disease subtypes. Red line shows aggregate random-effects ERR estimate.

- Although mean cumulative radiation doses were ≤ 0.2 Gy in most of studies, the small numbers of participants exposed at high cumulative doses (≥ 0.5 Gy) drive the observed trends in most cohorts with these higher dose groups

Driving Evidence for Low Doses < 0.5 Gy

Table 2. ERR coefficients for circulatory diseases as a result of exposure to low-level radiation ≥ 5 years earlier, by disease.

Disease	References	Fixed-effect estimate of ERR/Sv (95% CI)	Random-effect estimate of ERR/Sv (95% CI)	1-sided significance, p -value (fixed effect/random effect)	Heterogeneity χ^2 (df)/ p -value
IHD (ICD-10 I20–I25)	Azizova et al. 2010a ^a , Ivanov et al. 2006, Lane et al. 2010, Laurent et al. 2010, Muirhead et al. 2009, Shimizu et al. 2010, Vrijheid et al. 2007, Yamada et al. 2004	0.10 (0.05, 0.15)	0.10 (0.04, 0.15)	< 0.001/< 0.001	7.20 (7)/0.408
Non-IHD (ICD-10 I26–I52)	Ivanov et al. 2006, Shimizu et al. 2010 ^b , Vrijheid et al. 2007 ^c	0.12 (–0.01, 0.25)	0.08 (–0.12, 0.28)	0.031/0.222	4.65 (3)/0.199
CVA (ICD-10 I60–I69)	Azizova et al. 2010b ^d , Ivanov et al. 2006, Kreuzer et al. 2006, Lane et al. 2010, Laurent et al. 2010, Muirhead et al. 2009, Shimizu et al. 2010, Vrijheid et al. 2007, Yamada et al. 2004	0.20 (0.14, 0.25)	0.21 (0.02, 0.39)	< 0.001/0.014	34.28 (8)/< 0.001
Circulatory disease apart from heart disease and CVA (ICD-10 I00–I19, I53–I59, I70–I99)	Ivanov et al. 2006 ^e , Shimizu et al. 2010 ^f , Yamada et al. 2004 ^g	0.10 (0.05, 0.14)	0.19 (–0.00, 0.38)	< 0.001/0.026	66.83 (7)/< 0.001

Values are from Table 1, unless otherwise indicated.

^aAnalysis based on morbidity from IHD, with a 10-year lag. ^bAnalysis based on mortality from heart failure and other heart disease. ^cAnalysis based on mortality from heart failure.

^dAnalysis based on morbidity from CVA, with a 10-year lag. ^eAnalysis based on morbidity from hypertension, disease of arteries, arterioles and capillaries, veins, lymphatic vessels, and lymph nodes. ^fAnalysis based on mortality from rheumatic heart disease and circulatory disease apart from heart disease and CVA. ^gAnalysis based on morbidity from hypertension, hypertensive heart disease, and aortic aneurysm.

- Suggests increased risks for IHD and non-IHD heart diseases
- Data suggest that circulatory disease risk is significantly elevated only for acute or cumulative doses of about **0.5 Gy and above**; data is not statistically significant at lower doses.

Low Dose Confounders & Uncertainties

- **Confounding factors in epidemiology studies** include (Lifestyle and genetic factors): male sex, family history, cigarette smoking, drinking, diabetes, high blood pressure, obesity, increased low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol plasma levels; shift work
- Risk at lower doses and low dose rates still highly uncertain; **existence of threshold dose questionable**
- There is also a lack of data on **dose rate effects**



Latest ICRP Recommendations (ICRP 2012)

Definition of “Threshold Dose”:

- Previous NCRP 2000 Report defined a “threshold dose” as an exposure below which clinically significant effects do not occur
- ICRP 2012 redefined “threshold dose” as ED1 (estimated dose for 1% incidence), denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation.
 - ED1 = effects just starting to rise above the baseline levels in unirradiated, age-matched individuals and, in the case of circulatory disease, to a dose which would increase the already high natural incidence or mortality by only 1%.
- ED1 does not imply that no biological effects occur at lower doses; it merely defines the dose above which a specified effect becomes clinically apparent in a small percentage of individuals.

Latest ICRP Recommendations (ICRP 2012)

- **0.5 Gy** may lead to approximately 1% of exposed individuals developing the disease in question >10 years after exposure. This is in addition to the high natural incidence rate (circulatory diseases account for 30–50% of all deaths in most developed countries).
- There are notable uncertainties in determining the risks of these diseases at this level of radiation dose. It is **unclear from available evidence whether or not the threshold is the same for acute, fractionated, and chronic exposures**. For the present purposes, the threshold dose is assumed to be the same for all three types of exposure (i.e. approximately 0.5 Gy).

Dose Rate Effects

- Tuberculosis patients in Canadian Fluoroscopy Cohort Study
- 63,707 patients (61% unexposed, 96% <0.5 Gy, mean dose=0.79 Gy)



Table 6. Excess Relative Risks per Gy for Noncancer Causes of Death by Categories of Dose Fractionation, Canadian Fluoroscopy Cohort Study, 1950–1987

Cause of Death	Dose Fractionation, Gy/year ^a										P Value ^b
	0	0.0004–0.14			0.15–0.29			0.30–7.30			
	No. of Deaths	No. of Deaths	ERR/Gy ^c	95% CI	No. of Deaths	ERR/Gy ^c	95% CI	No. of Deaths	ERR/Gy ^c	95% CI	
All noncancer ^d	8,299	810	0.168	−0.179, 0.617	940	0.069	−0.017, 0.173	2,886	0.034	−0.006, 0.080	0.569
All CVDs	5,696	569	0.281	−0.139, 0.848	650	0.089	−0.017, 0.219	1,962	0.021	−0.025, 0.077	0.241
Ischemic heart disease	3,716	391	0.592	0.004, 1.400	442	0.145	0.007, 0.320	1,269	0.010	−0.043, 0.078	0.022
Hypertensive and other (nonstroke) CVDs	1,078	106	0.381	<−0.198, 1.953	120	−0.069	<−0.099, 0.187	393	0.035	−0.059, 0.177	0.447
All respiratory diseases	1,694	179	0.645	<−0.200, 2.114	186	−0.0002	<−0.117, 0.225	599	0.093	0.006, 0.214	0.299

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ERR, excess relative risk.

^a The 4 dose fractionation groups are equivalent to the following numbers of fluoroscopic procedures per year: 0, >0–11, 12–23, and 24–584.

^b *P* for heterogeneity from the likelihood ratio test.

^c All analyses are adjusted for categories of sex, attained age, calendar year, Canadian province of admission, type (pulmonary vs. nonpulmonary) and stage of tuberculosis diagnosis, and duration of fluoroscopy screenings by stratification.

^d Excludes deaths attributed to tumors that were benign or of uncertain nature, infectious diseases, and external causes.

- ERR/Gy=0.176 for IHD after adjustment for dose fractionation. ERR/Gy=0.149 for doses <0.5 Gy
- Highest risks were for those with fewest fluoroscopic procedures per year

Potential Mechanisms for Radiation-Induced CVD

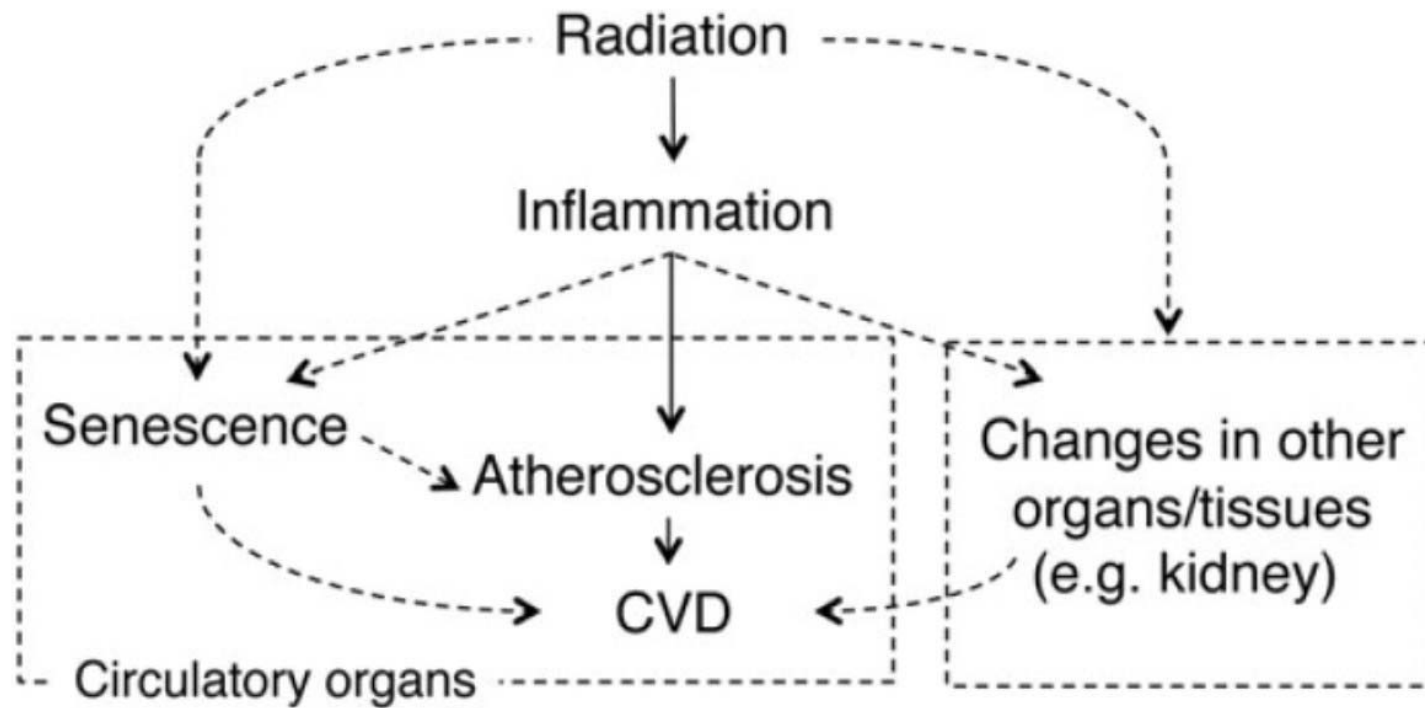


Fig. 6. Hypothetical mechanisms of radiogenic CVD. Solid arrows represent the inflammation theory. Dashed arrows represent hypotheses discussed here.

Potential Mechanisms for Exposures from Moderate Doses

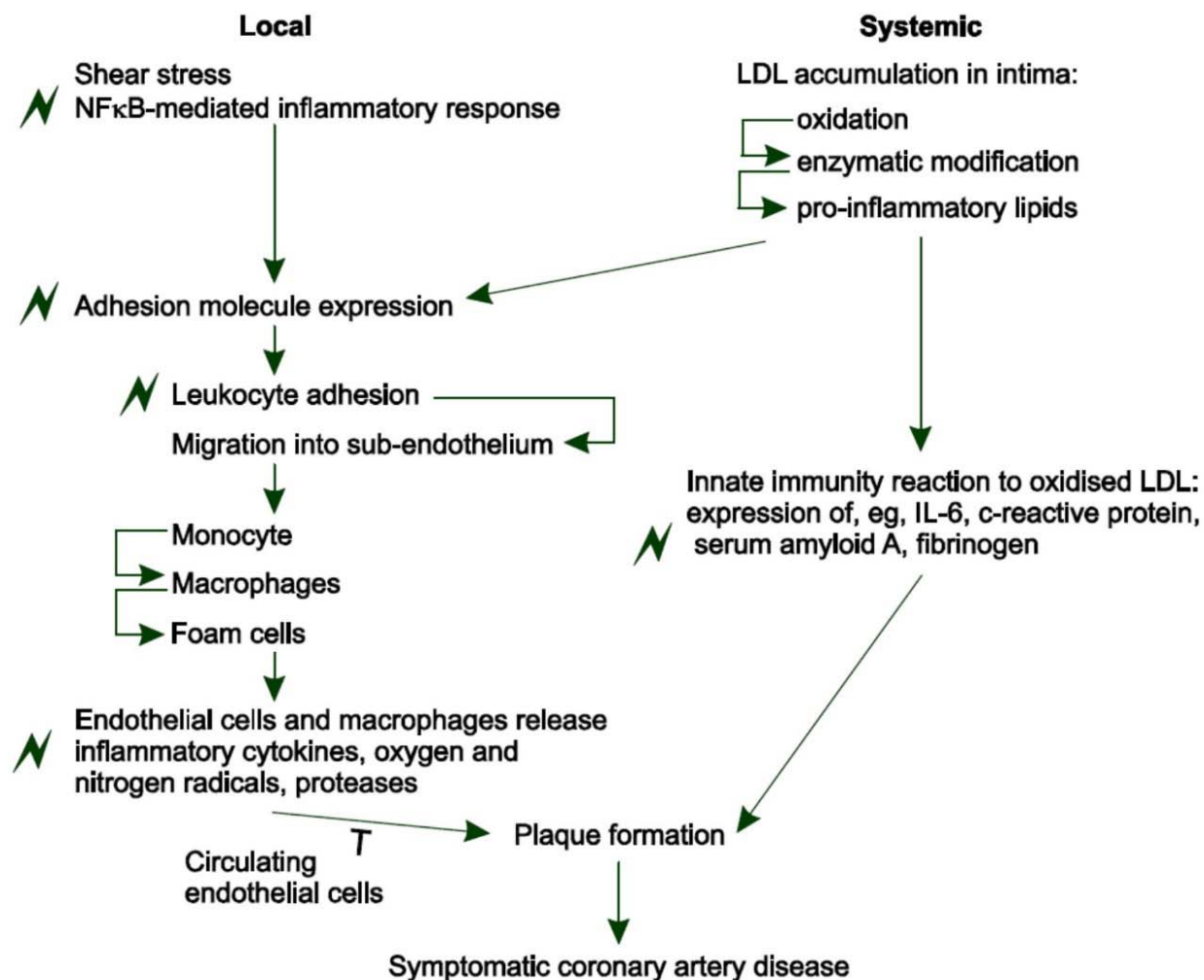


FIGURE 6.1 Schematic representation of the most important steps of pathogenesis coronary artery disease. Events that have also been observed after radiation exposure are indicated by flashes. (From Schultz-Hector and Trott, 2007)

Kidney Dysfunction & CVD

TABLE 5
Odds Ratio (95% Confidence Interval) of Radiation Dose for Chronic Kidney Disease (CKD)

Renal dysfunction	<i>n</i>	Not adjusted OR/Gy (95%CI)	<i>P</i>	Adjusted ^a OR/Gy (95%CI)	<i>P</i> ^a
Normal–mild	584	1		1	
Moderate	149	1.13 (0.90–1.44)	0.295	1.15 (0.89–1.48)	0.293
Severe	13	2.25 (1.36–3.78)	0.002	3.19 (1.63–6.25)	<0.001
CKD (moderate + severe)	162	1.26 (1.01–1.57)	0.040*	1.29 (1.01–1.63)	0.038*

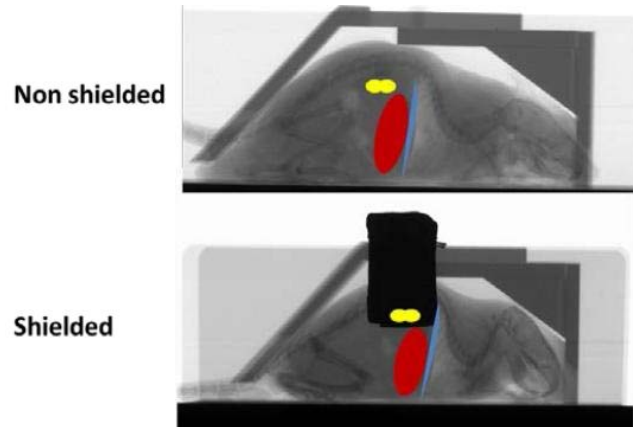
Notes. Reference was the combined normal and mild renal dysfunction group. CKD; chronic kidney disease.

^aAdjusted for age, gender, and smoking and drinking habits, hypertension, diabetes mellitus, hyperlipidemia and metabolic syndrome.

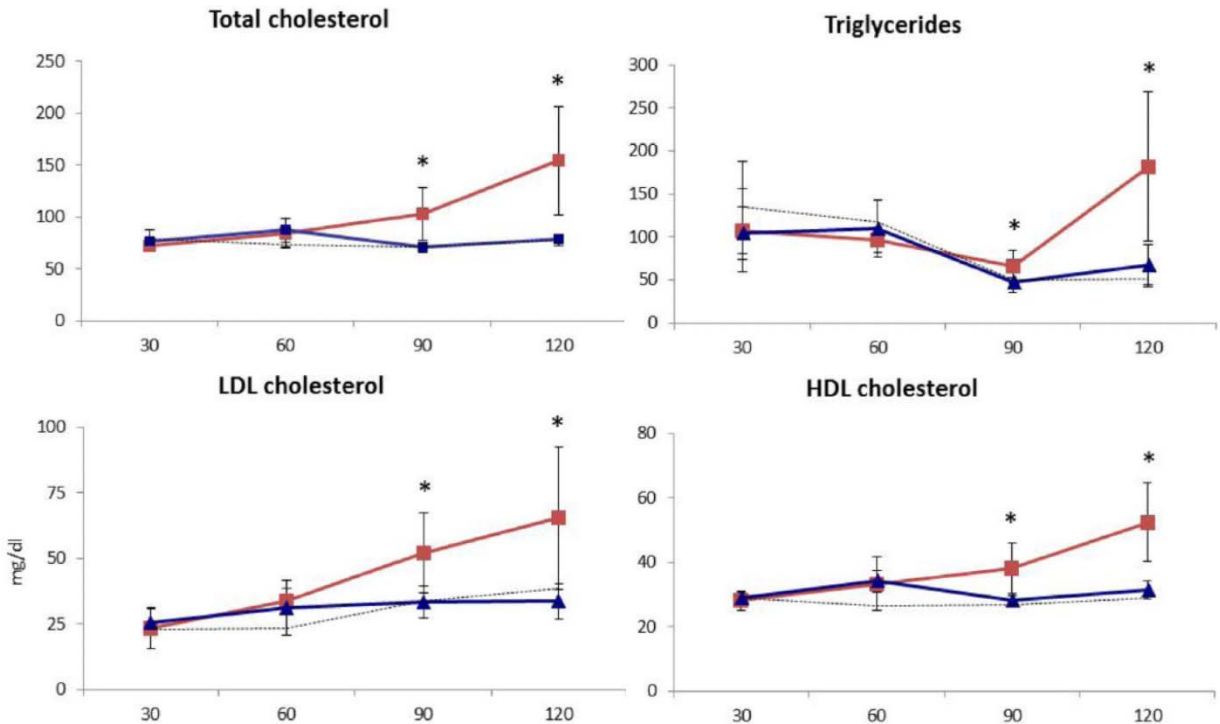
*Analyzed with ordinal logistic regression model.

- Cohort of atomic bomb survivors in the Life Span Study
- Results show low dose radiation was significantly associated with CKD and severe renal dysfunction independently of hypertension, DM, hyperlipidemia and MetS, suggesting that A-bomb radiation affects the kidney directly.
- Prospective studies are needed to clarify how the association between low-dose radiation and CVD may be mediated by CKD.

Kidney Dysfunction & CVD



The location of the kidneys (yellow) and liver (red) are indicated. The liver lies directly under the diaphragm (blue), which separates the thoracic and abdominal cavities. In this lateral image, the two kidneys are overlapping with the left kidney being the more caudal than the right kidney.



Time-related changes in total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol TBI with and without kidney shielding compared with sham irradiated controls. Data shown as means + SD, n=5-8/group. * = p < 0.05, TBI vs. TBI with the kidneys shielded.

■ = TBI lateral, ■ = lateral TBI with the kidneys shielded
●●●●●●●● = sham-irradiated control.

➤ **Kidney shielding during IR prevents increase in risk factors for heart disease**

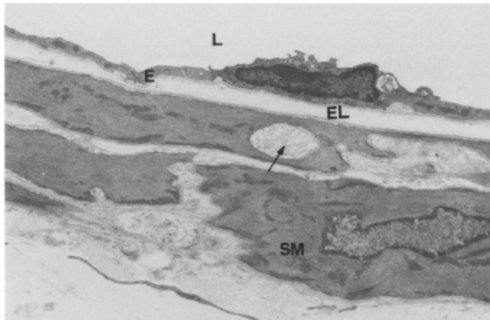
Major Risk Questions

- Radiation quality effects?
- Deterministic versus stochastic effects? Existence of thresholds?
- Dose rate effects?
- Validated/appropriate biomarkers?
- Disease spectrum is unclear for doses of interest
 - Necessity for life span studies in an appropriate animal model to determine spectrum of diseases, at low dose rates, with heavy ions
- What are appropriate endpoints?
- What's the appropriate animal model?

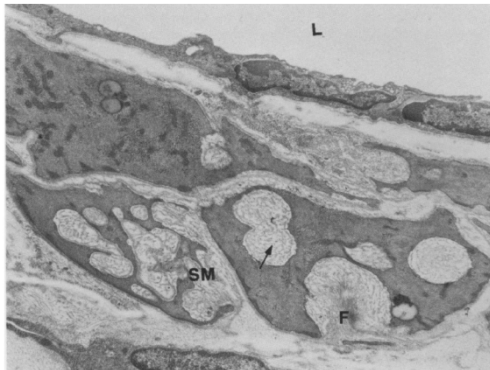
Research Evidence Updates

Late Effects of Heavy Charge Particles on Fine Structure of Mouse Coronary Artery Yang and Ainsworth 1982

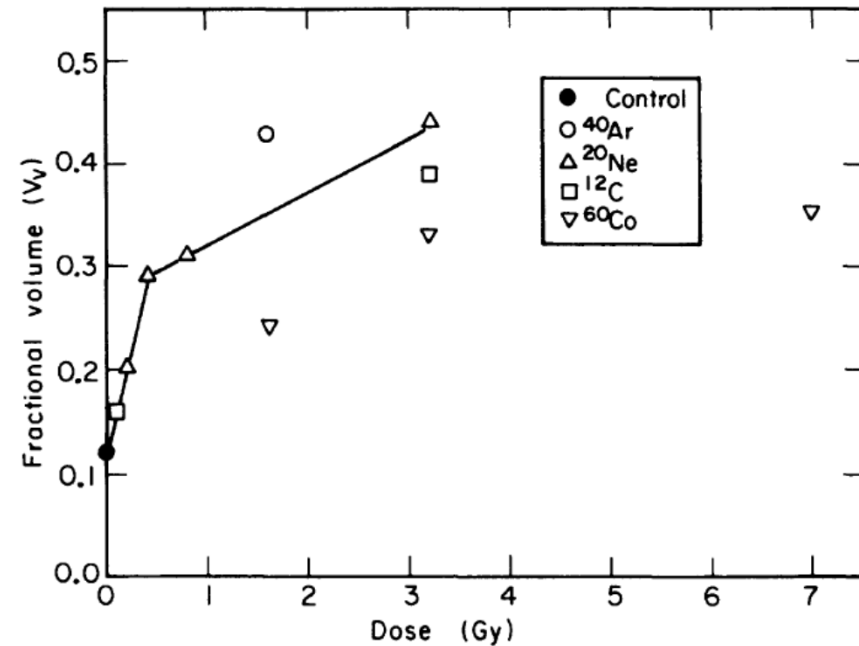
Control



^{20}Ne (0.2 Gy)



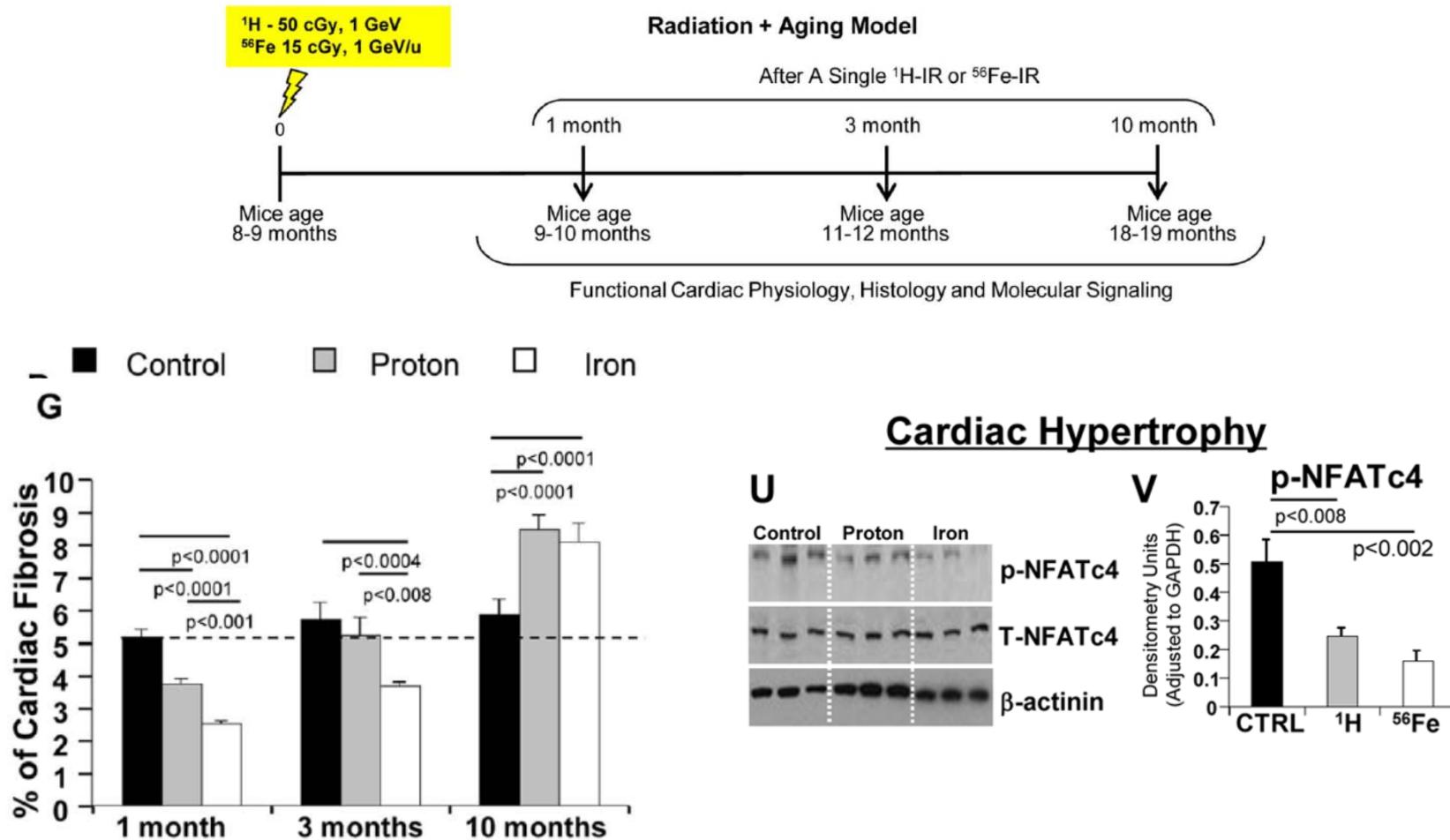
Ultrastructural changes in the coronary artery at 15 months after 0.2 Gy ^{20}Ne upper body IR. Fragmentation of smooth muscle (SM) with accumulation of matrix material (arrow) and fibrosis (F) are noted. Lumen (L) and elastic lamina (EL). x6480.



Dose-response relationship for damaged smooth muscle cells after heavy charged particle irradiation.

- Degenerative changes included smooth muscle degeneration and accumulation of tissue debris and fibrosis
- Low dose, heavy ion radiation accelerated these degenerative changes
- Intimal plaques also observed, but without lipid bodies found in atherosclerosis

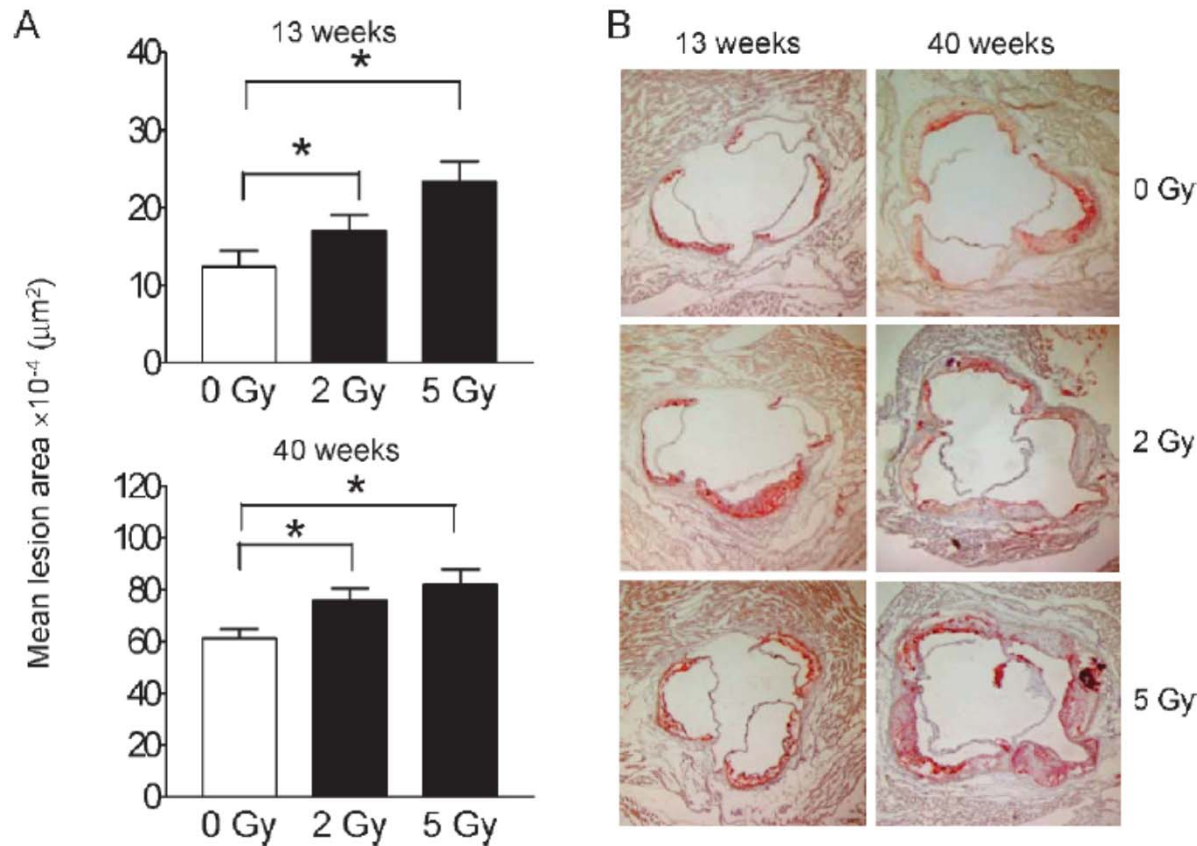
Cardiovascular risks associated with low dose ionizing particle radiation. Goukassian et al. 2014



- Cardiac fibrosis and hypertrophy still observed at late time points (up to 10 months) after IR with both Fe and protons

Heavy-Ion (^{56}Fe) Irradiation Leads to Impaired Aortic Relaxation and Accelerated Atherosclerosis in ApoE $^{-/-}$ Mice.

Kucik et al. 2011, 2014



- Fe irradiation at 2 and 5 Gy doses in 9-week-old apoE $^{-/-}$ mice
- Irradiation **accelerated atherosclerosis at the aortic root** and effects was still seen up to 40 weeks post-irradiation (Kucik et al, Rad Res 2011)

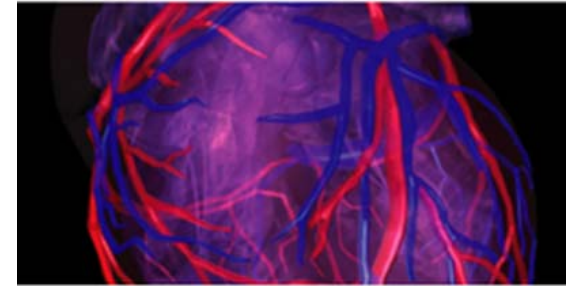
- Fe radiation at 2.6 Gy in 10-week-old apoE $^{-/-}$ mice; 4-5 weeks after IR, saw **significantly impaired vascular relaxation** in response to acetylcholine (Kucik et al, JRR 2014)

Yu and Kucik 2011 - Rad Res v175 p766 - Iron-Ion Radiation Accelerates Atherosclerosis in Apolipoprotein E-Deficient Mice

White and Kucik 2014 - J Rad Res v55 pi42 - Heavy-Ion (^{56}Fe) Irradiation Leads to Impaired Aortic Relaxation prior to Atherosclerotic Plaque Formation in ApoE $^{-/-}$ Mice.

CVD Risk Summary

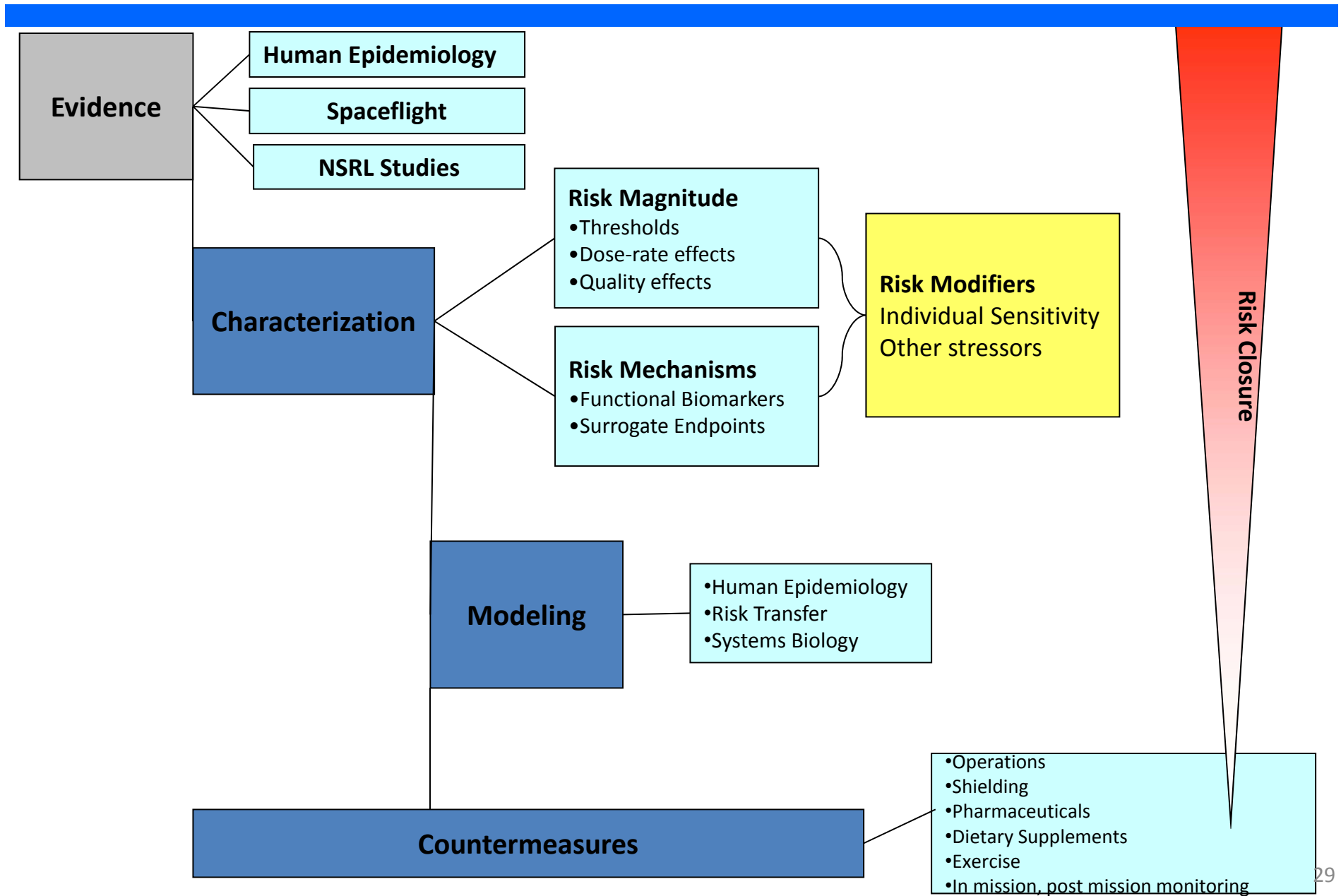
- Association between exposure to high doses of low-LET (>5 Gy) radiation during radiotherapy to the chest and increased risk for development of cardiovascular disease at late times post exposure is clearly established
- Recent studies of atomic bomb survivor data and analyses of epidemiology data from occupational and medical exposures provide evidence for elevation of risk at lower doses than previously identified, with **significant risks at doses as low as 0.5 Gy**
 - Data at low doses is **confounded by life-style factors, clouding interpretation of epidemiology data below 0.5 Gy**
 - Effects are **considered deterministic, with an associated threshold dose; however recent evidence showing risk at lower doses questions this assumption**
- Preliminary risk assessment models are being formulated based on recent epidemiology data for lower dose low-LET exposures - future risk estimates dependent on research results describing the quantitative and qualitative differences between GCR and gamma-rays
 - Studies at NSRL with HZE ions and **appropriate animals models are required**
 - **Lack of evidence on radiation quality, disease spectrum, latency and dose rate at low levels of exposures**
- **The additional mortality and morbidity risks for non-cancer diseases of the cardiovascular system are major concerns because they could increase REID values substantially**



STRATEGY

Exposure to Space Radiation

Research Strategy for Risk Mitigation



Degenerative Gaps

- Degen - 1:** How can tissue specific risk models be developed for the major degenerative tissue risks, including heart, circulatory, endocrine, digestive, lens and other tissue systems in order to estimate GCR and SPE risks for degenerative diseases?
- Degen - 2:** What are the mechanisms of degenerative tissues risks in the heart, circulatory, endocrine, digestive, lens and other tissue systems? What surrogate endpoints do they suggest?
- Degen - 3:** What are the progression rates and latency periods for degenerative risks, and how do progression rates depend on age, gender, radiation type, or other physiological or environmental factors?
- Degen - 4:** How does individual susceptibility including hereditary pre-disposition alter degenerative tissue risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?
- Degen - 5:** What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?
- Degen - 6:** What are the most effective biomedical or dietary countermeasures to degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?
- Degen - 7:** Are their significant synergistic effects from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?
- Degen - 8:** Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?

Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation

Three Phase Implementation:

1. **Phase 1**: Develop biological models, investigate existence of dose thresholds for CVD effects, investigate mechanisms, define radiation quality effects and dose-rate effects
 - Through individual NRAs and the NSBRI CSRR
2. **Phase 2**: Investigate latency periods, progression rates, and individual susceptibility effects
 - Through individual NRAs and the NSCORs
3. **Phase 3**: Identify biomarkers and countermeasures for CVD and investigate potential synergies with other spaceflight factors.
 - Through individual NRAs and a countermeasure NSCOR

Degenerative Risk Summary

Overall, there is a paucity of experimental data related to radiation-induced heart diseases at low doses:

- **Qualitative differences** between GCR and gamma-rays are major concern
- **Deterministic versus stochastic effects** is unknown at doses <0.5 Gy.
- Impact of **dose rate**
- A concern for **Mars or lunar missions** due to higher GCR and SPE doses with definitive effects
- Recently established NSBRI **Center for Space Radiation Research** will focus on cardiovascular risk research
- Can **cataract monitoring in astronauts** provide insight into radiation quality effects, progression, and latency, specifically for space radiation exposure in humans?
- For relevant space radiation doses, can **cataracts and kidney dysfunction be related to other radiation-induced pathologies** including CVD?

